



Coordination of Programs on Domestic Animal Genomics: A Federal Framework

National Science and Technology Council • Committee on Science
Interagency Working Group on Domestic Animal Genomics

September 2003

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EXECUTIVE OFFICE OF THE PRESIDENT
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
WASHINGTON, D.C. 20502

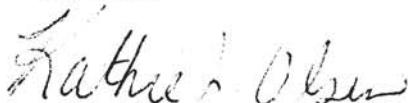
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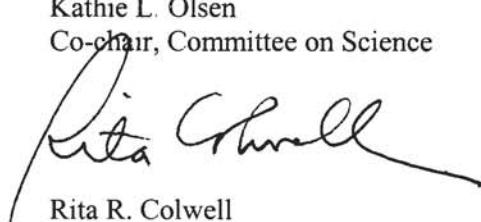
This report provides a five-year plan for Federal agencies dealing with genomics activities related to domesticated animals. This plan was developed by the National Science and Technology Council Committee on Science's Interagency Working Group (IWG) on Domestic Animal Genomics. The IWG was chartered in March 2002 to raise awareness of the importance of domesticated animal species and address and coordinate Federal programs in domestic animal genomics. The IWG held listening sessions with both scientists and industry representatives to obtain facts and information prior to developing this plan.

It is clear that a more complete understanding of domesticated animal genomes will have broad reaching impact, from illuminating evolutionary relationships to facilitating the understanding of human disease and the development of new therapeutics and increasing food quality, safety, and yield. With active domestic and international genomics efforts on humans, research model animals (e.g., fly, nematode, rat, and mouse), plants, and microorganisms well under way, it is time for Federal agencies to focus their attention on the genomes of domesticated animals as well.

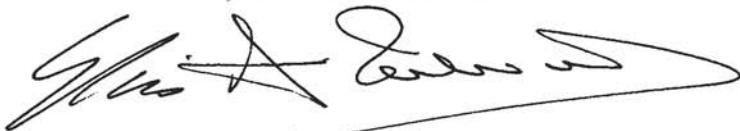
Sincerely,



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Co-chair, Committee on Science



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Co-chair, Committee on Science



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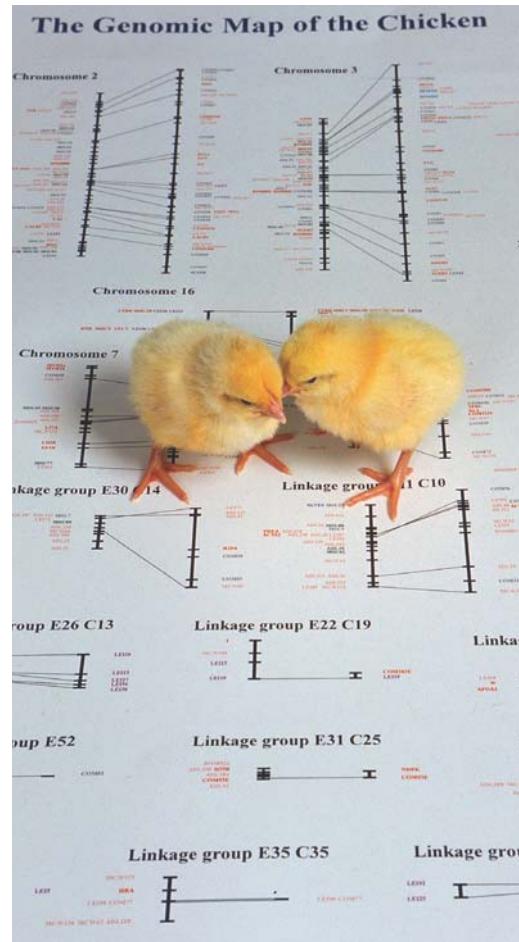
Coordination of Programs on Domestic Animal Genomics: A Federal Framework

Executive Summary

The Interagency Working Group (IWG) on Domestic Animal Genomics was chartered in March 2002 to enhance communication and awareness of the importance of domesticated animals, both livestock and companion, as a critical part of the Federal genomics programs. The U.S. Department of Agriculture, National Institutes of Health, National Science Foundation, and U.S. Department of Energy all support programs in genomics, from genome research tools and large-scale genome sequencing to bioinformatics and functional genomics.

Domesticated animals play a central role in the food supply as well as biomedical research. With the high quality genome sequences of human, microbes, and plants, as well as other model organisms already available, obtaining similar scientific research resources for both livestock and companion animals will contribute significantly to improvements in the food supply, human health, and the economy. The increased diversity of genomes will allow comparative studies to identify new genes, understand the evolutionary relationships among species, and generate data central to understanding disease susceptibility and food production. Healthier and more efficient livestock impact the safety, security, and abundance of foods. Increased knowledge of domesticated animals commonly used to study human biology and diseases will benefit human health and the development of new pharmaceutical products.

With significant input from Federal agencies currently investing in genomics, members of the scientific community, and industry, the IWG outlined a mission and developed a five year framework for Federal support of domestic animal genomics. The framework will facilitate coordination of several agencies to maximize use of resources to produce the genome sequences of the most important domesticated animal species, support data management, bioinformatics, and functional genomics specific for livestock and companion animals.



I. Introduction

Domesticated animals have played a key role in human society through their use in agriculture, medical research, and as human companions. The completion of the human genome DNA sequence in April 2003 marks an important milestone in scientific knowledge and the research arising from it, called genomics, provides a new opportunity to improve and understand domesticated animals. Once a genome sequence is in hand, scientists use it to identify new genes, discover and understand regulatory elements in the non-coding regions of the genome, and study individual genes, their functional products on a molecular level and their interactions with other genes. Genome sequencing projects are underway for several animals (including mice, rats and fish) that serve as models for studying human disease. Projects for other important models, including domesticated animals, are being considered.

Domesticated animals include both livestock and companion animals, e.g. cattle, swine, sheep, chicken, fish, honeybee, cat, dog, and horse. It is anticipated that genomic studies of livestock animals will yield an understanding of the genetics and expression of genes important to improving the species for greater food yields. The inclusion of domesticated animals in a Federal genomics program serves two purposes: 1) to increase the diversity of genomic sequence available for comparative studies that contribute to finding new genes and studying evolution; and 2) generate data critical to understanding disease susceptibility and food production.

In the United States, livestock and companion animals are the backbone of billion dollar industries. Measures taken to improve the agricultural outputs will benefit the U.S. industry as well as enable larger human populations to improve nutrition, sustain populations in challenging environments, and address specific environmental and biosecurity threats. The biomedical research industry will gain from advances in understanding human biology based on insights from a diversity of species, and it is anticipated that it will accelerate the development of new pharmaceuticals.



II. Background

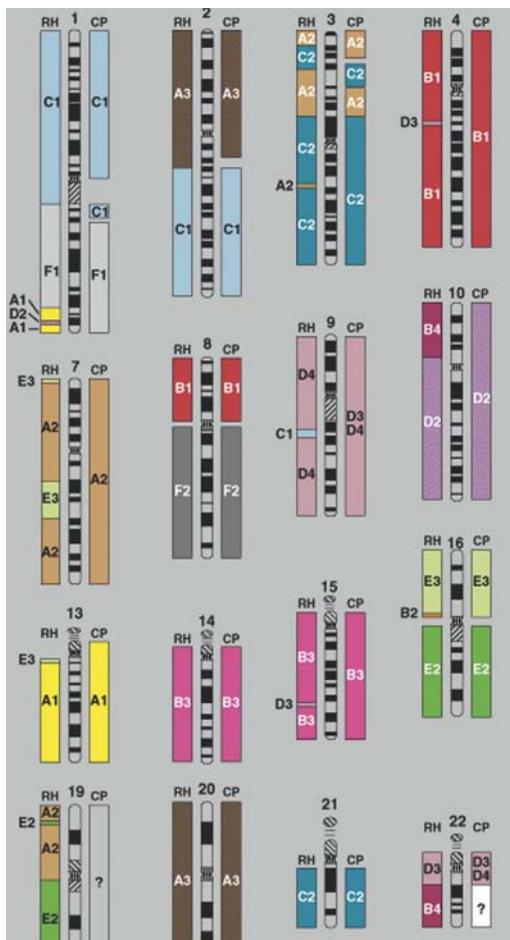
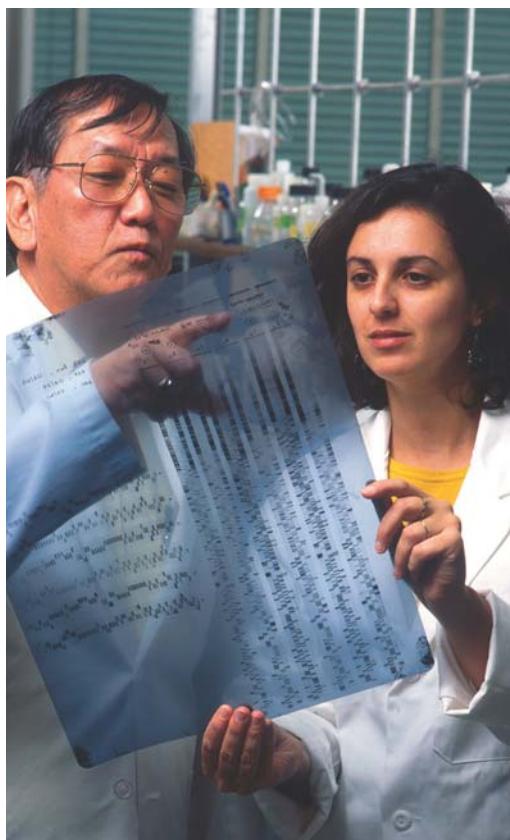
The Interagency Working Group (IWG) on Domestic Animal Genomics was chartered on March 14, 2002, by Dr. John Marburger III, Director of the Office of Science and Technology Policy, following a January 2, 2002 presentation to the Committee on Science of the National Science and Technology Council by Dr. Joseph Jen, Under Secretary for Research, Education, and Economics, U.S. Department of Agriculture. The charge to the IWG was to enhance interagency communication and awareness of the importance of agricultural species, to increase leverage of investments across government agencies, and to position agriculture as a critical element of the Federal genomics programs. The Committee on Science provides oversight over the IWG activities. The membership of the IWG consists of representatives from the Department of Agriculture (USDA), Department of Energy (DOE), Food and Drug Administration (FDA), National Institutes of Health (NIH), National Science Foundation (NSF), Office of Science and Technology Policy (OSTP), Office of Management and Budget (OMB), and U.S. Agency for International Development (USAID).

Upon convening, the initial deliberations regarding the task set forth to the IWG led to an overarching statement of purpose:

The mission of the Interagency Working Group for Domestic Animal Genomics is to enhance communication and awareness of livestock and companion animal species of importance to the food and agriculture system, leverage Federal investments in large-scale genome sequencing and genome analysis across government agencies, position food and agriculture system as a critical element of the national genomics program, and enhance dialogue and cooperation among Federal agencies, universities, and industry in the nation, and promote international cooperation on domestic animal genomics research.

The IWG has also outlined a number of strategic goals:

- Bring into place the programmatic elements needed to advance the study and understanding of domesticated animal genomes, including large-scale DNA sequencing; functional characterization of expressed genes (functional genomics); tools for data storage, analysis and visualization (bioinformatics); and study of similarities among genomes of different species (comparative genomics).
- Leverage the national infrastructure for large-scale DNA sequencing that has been established for the Human Genome Project and other vertebrate and model organism genomes.
- Advance and utilize the enabling tools and infrastructure of functional genomics and bioinformatics to enhance the understanding not only of basic science and disease mechanisms, but also to address critical agricultural missions, including animal health and well-being, food safety, and human nutrition.
- Ensure that genomics data are freely available in the public domain and genomics reagents and resources are available to the public.
- Increase the training opportunities for genomics and bioinformatics at all levels of education.
- Coordinate and encourage international cooperation to achieve these goals.





III. Rationale for investment in a domestic animal genomics program

The anticipated wide-ranging benefits of a domestic animal genomics program were apparent from a National Research Council-sponsored workshop, *Exploring Horizons for Domestic Animal Genomics*, and two subsequent IWG meetings with stakeholders (including representatives from industry and the research community). In addition, the Alliance for Animal Genome Research (an advocacy group representing universities, scientific societies, and industry) has clearly outlined the benefits in their white paper, *The Animal Genome Initiative: Advancing Human and Animal Health*. These benefits can be summarized as follows:

- Comparative genomics: The biomedical research community will benefit from all animal species that have been proposed for genome sequencing. Comparative genomics, utilizing diverse species' genomes, facilitates genome annotation and increases the understanding of the human genome, both for genes as well as intragenic regions, and increases opportunities to identify disease-causing genes.
- Study of human disease: Domesticated animals, particularly dogs and cats, commonly acquire illnesses that can be studied as models for human diseases. They are widely used to study diseases such as cancer, HIV/AIDS, epilepsy, and heart disease.
- Study of human biology: Basic understanding of the immune, endocrine, and cardiovascular systems, as well as embryonic development, have come from the study of domesticated animals, including chicken, dog, and pig.
- Biomedical applications: Livestock research has contributed to developments in the study of interventions for human diseases through serving as models for xenotransplantation (tissue transfer from one organism to another) and in vitro fertilization. Several species of domesticated animals are potential "bioreactors," genetically engineered animals that produce pharmaceuticals as well as tissues and organs that would be safe for human transplant. Finally, the availability of detailed genomic information will assist in the evaluation of the safety and efficacy of new products by the regulatory authorities.
- Public access to genome resources and data: There is considerable private sector interest in improvements in food production and development of treatments for diseases. Genomics research within the private sector is likely to be targeted at profitable traits and possibly proprietary. Publicly funded genomics programs for other genomes (including human and plant) have ensured that all researchers have access to complete sets of data and tools, and this policy is important to continue for domesticated animal genomes as well.

The domestication of animals as livestock and for companionship has long relied on traditional breeding methods that enhanced desirable traits and created specialized food sources, such as dairy and beef cattle. There is a wealth of collected quantitative trait loci (QTL), measurable traits (e.g. milk production and disease resistance) that are controlled by multiple genes and some of which have been localized to specific chromosomal regions. The availability of genome sequences will facilitate the identification and study of the genes influencing important traits, the underlying regulatory control elements, and the gene products on a molecular level.

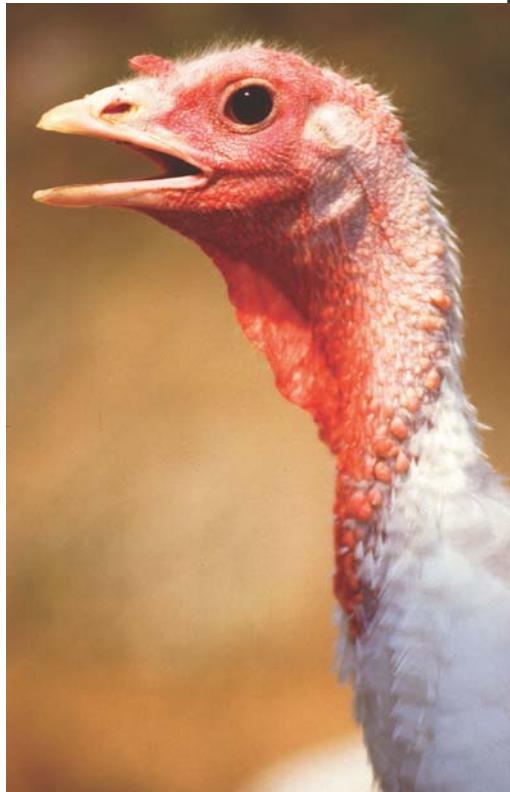
Research on domesticated animals will benefit from genomic resources and tools that are currently available to scientists studying humans and model organisms, thereby reducing the time necessary to identify and study a gene responsible for higher quality food products. The availability of the most innovative and efficient tools for agriculture research, equivalent to

those for biomedical research, will increase the attractiveness of agriculture as a research investment and attract and retain the best scientists in the agriculture research sector. Significant insight will be gained in numerous areas, including food production efficiency, host-pathogen interactions, and instinctive behaviors. Benefits will encompass increased food safety and security, higher quality food for lower cost, reduced environmental impact, greater economic competitiveness, and novel products containing additional nutritional and health benefits. The translation of genomic research to improved livestock yield will have a positive effect on the small scale farming industry by providing the means to increase efficiency in producing superior food products.

Sequencing the genomes of a broad array of animals will additionally impact the basic understanding of the diversity of species. Comparative genomics can yield information about phylogenetic proximity and genome organization that leads to insight into the process of evolution. The research will also illuminate the contribution of genes to defining unique species. To date, out of 18 modern mammalian orders, only human (Primate), and mouse and rat (Rodentia) have been sequenced or are underway. Expansion to include genomic studies of livestock and companion animals will contribute substantial diversity. The genome sequences of chicken and fish, as non-mammalian domesticated animals, will introduce yet greater diversity in evolutionary research. As the first bird genome to be sequenced, the chicken genome will provide important information about the evolution of vertebrates as well as genetic information that can be used to improve the agriculturally important traits of the species. Studying the genome sequence of the honeybee may provide new insights into genes that control or contribute to social behavior of insects that may provide knowledge that will improve the agricultural yield of these interesting insects.

Greater understanding of species on a genomic level will also have additional environmental benefits. The honeybee has shown potential to serve as a biosensor and trout have historically proven to be sensitive to chemical pollutants. In the wake of the anthrax attacks of 2001, the elevated interest in tools for biomonitoring for chemical and biological agents, as well as for preventive and therapeutic treatments, reflects an additional application for animal genomics research.

While this research has tremendous potential to affect our health, our food sources, and our economy, the translation from genome sequence to a marketable product is a long term process. Since genomics is fast becoming a mainstay of basic research across numerous disciplines, it is imperative that the information continue to remain free and accessible to the public. The Federal government has a unique and valuable role in supporting such endeavors that are unlikely to be undertaken by industry.



IV. U.S. Federal investment in domestic animal genomics

Federal investment in animal genomics from DOE, NIH, NSF, and USDA covers the full range of genomic resources, from expressed sequence tag (EST) libraries and bacterial artificial chromosome (BAC) libraries to large-scale genome sequencing, genome annotation, data management, bioinformatics, and functional genomics. Table I highlights the recent and proposed Federal investment by DOE, NIH/NHGRI, NSF and USDA in pre- and post-sequencing resources, large-scale sequencing, and functional genomics. The knowledge, experience and tools developed for earlier and ongoing projects on other organisms translate to lowered costs, improved data quality, and the development of basic tools that allow scientists to access and utilize the data. As examples of non-domesticated animal research funding, the NSF and NIH have both made major general contributions to functional genomics, and support data management and informatics tools. The investment in databases and resources will serve as platforms in domestic animal genome research.

Table I. Federal investment in domestic animal genomics.

The figures encompass pre-and post-sequencing resources (e.g. BAC and EST libraries, deletion and marker insertion strains), large-scale sequencing, and functional genomics directly related to domesticated animals. Funds appropriated for fiscal year 2003 may change to reflect competitive grant awards. Funding shown for fiscal year 2004 is consistent with the President's budget request. All figures are in thousands of dollars.

	FY01	FY02	FY03	FY04
DOE	N/A	60	60	N/A
NIH	3,835	7,520	62,606	42,946
NSF*	1,751	3,066	4,150	4,333
USDA	26,835	28,191	37,939	44,440
Total	32,421	38,837	104,755	91,719

* NSF funding represents investment in a broader array of animals.

Support of domestic animal genomics has been increasing and evolving within numerous agencies that have contributed to the human genome sequencing project and in sequencing numerous other organisms, including bacteria and plants. For example, the National Human Genome Research Institute at NIH supports large-scale genome sequencing of several organisms, including chicken and honeybee, and has significant investments in DNA libraries, data management, databases, bioinformatics, and functional genomics. In February 2002, NHGRI initiated a white paper process for soliciting nominations for the sequencing of new genomes. The dog and cow genomes are currently ranked as high priority genome sequencing targets. Several other species are being proposed as new sequencing targets, including cat and swine. NHGRI has indicated support for large-scale sequencing of several high priority domesticated animals, although there is no schedule as of yet. In addition, NHGRI will leverage opportunities to partner with Federal agencies, state governments, and private organizations with interests in agriculture.



The DOE Office of Biological and Environmental Research is currently sequencing targeted regions of the chicken genome that are similar to human chromosome 19. This is part of a functional and evolutionary comparison of multiple animal genomes with human chromosome 19, the smallest and most gene-dense. The overlap with the complete chicken genome funded by NHGRI will be complementary, utilizing data to confirm, identify, and reduce the need for multiple reads. NSF funds functional genomics research in honeybee, fish, and chicken. USDA directs much of its investment in genomics towards developing sequencing resources and functional genomics. It is also supporting data management, informatics, genome annotation, and large-scale sequencing of honeybee. Many of the livestock species being considered for sequencing have substantial genome resources developed through USDA-funded research.

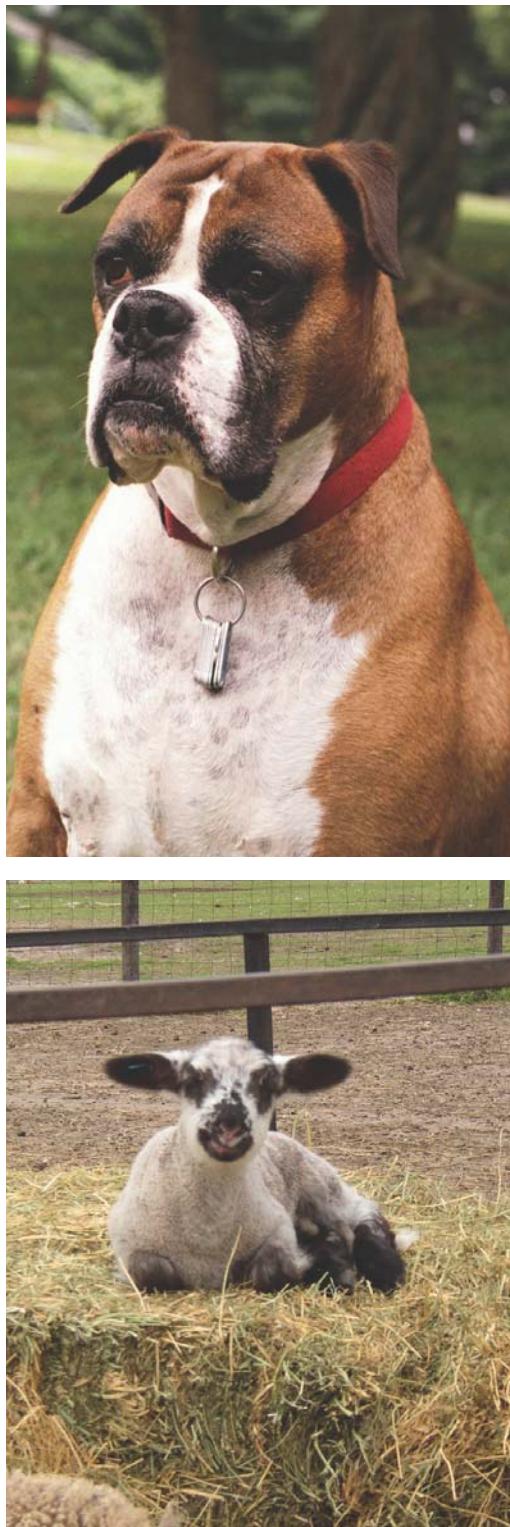
Each new genome that is sequenced also serves as an opportunity to improve the technology at the sequencing centers. Over the last 18 months, the cost of sequencing has undergone a two-fold reduction, and it is expected that with the introduction of new sequencing technology, another reduction of similar magnitude will occur over the next 18 months. The cost of whole genome shotgun sequencing of a mammalian genome (approximately 3 billion base pairs) at 8-fold genome coverage (an average of 8 reads per base of the sequence, also called a draft) was \$100 million in 2001; as of December 2002, the cost is approaching \$50 million (information communicated by the Human Genome Sequencing Center, Baylor College of Medicine). A finished sequence requires considerably more reads to fill in gaps, ensure correct orientation and order of genome fragments, further characterize remaining gaps in the genome, and yields a significantly reduced error rate. The cost of finishing a mammalian genome is an additional \$50-100 million. Draft sequence, however, provides ample information for comparative analysis and genome-wide research. Highly accurate sequencing may be done in targeted regions of interest to best address the scientific research as necessary.

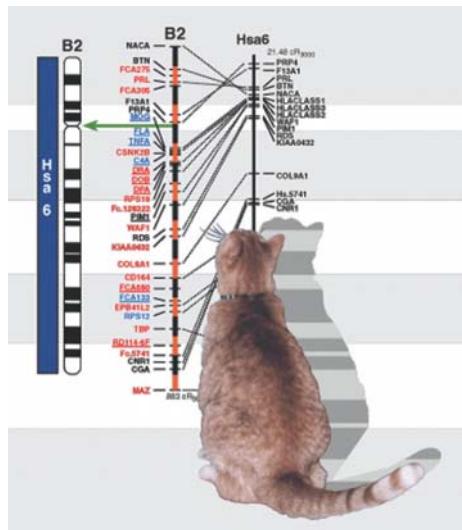
Beyond sequencing specific genomes, the IWG is also considering the necessary investments required for the ensuing data. Building on the resources currently in use, databases and bioinformatics tools will need to evolve as the amount of genome sequence data increases, and it is layered with functional information from many genomes. Long-term maintenance of databases and ease of using the data for a broad array of researchers requires continual attention to a strong bioinformatics program in parallel with a program in large-scale genome sequencing. The current bioinformatics investment by NIH and NSF is significant and covers a wide array of organisms.

The FY 2003 appropriation for domestic animal genomics is over \$94 million, which includes almost \$66 million for large-scale genome sequencing. This demonstrates a significant commitment to this endeavor. The increase of \$34.6 million over the FY 2002 appropriated funding level allows the sequencing of the chicken genome to continue, as well as initiating sequencing of other domesticated animal genomes. The President's FY 2004 budget request, at \$84.9 million, will continue to support genomic research on high priority animals. The smaller request in FY 2004 reflects improvements in technology that increase efficiency and reduce the cost of large-scale genome sequencing programs for selected high priority animals.

The interagency working group determined that large-scale sequencing, data management, bioinformatics, and functional genomics are the goals for fiscal years 2003 to 2007, including:

- Large-scale sequencing to produce draft genome sequences (8-fold sequence coverage) of honeybee, chicken, dog, cattle, swine, and cat.





- Data management and bioinformatics to specifically support agriculturally important species. This will support significant improvements in data management and analysis software, allow greater data accessibility and secure long term maintenance, increased capabilities to deal with rapidly accumulating data complexity as databases include functional information, more powerful tools to mine large genomes individually and for comparative genomics.
- Functional genomics to specifically investigate agriculturally important species. An increase in data for livestock genomes requires concomitant investment in functional genomics to support genome annotation, the study of gene regulation and expression, and species evolutionary relationships. Researchers will have access to individual genes, which can be cloned and characterized, the ability to scan entire genomes for specific functions, and be able to gain new insights from comparisons to other genomes. Quantitative trait loci will be accessible on a gene level, leading to studies that will elucidate characteristics such as food productivity and disease resistance and will lead to the ability to manipulate those traits more quickly and effectively.



V. International efforts

The human, mouse, rice, and *Arabidopsis* genome sequencing projects all exemplify the importance of international scientific cooperation. At the time these were initiated both projected costs and time to completion were significantly larger and longer. Today, a single genome sequencing center in the United States is capable of completing a draft sequence of a three billion base pair genome (the size of a large mammal) in 12 months. Collaboration remains highly valued. For example, future cooperative endeavors may maximize efficient use of resources by parsing out species for sequencing, library development, mapping and annotation activities.

VI. Conclusion

Long-term vitality of research on domesticated animals and their role in the broader understanding of human biology and evolution relies on the investment of a full spectrum of genome sciences. Scientists in the public and private sectors have expressed tremendous enthusiasm for investment in domestic animal genomics, and urged the IWG to take advantage of current momentum in genome sciences and Federal programs supporting genomics for other organisms. These tools will facilitate scientific discovery, attract and maintain bright researchers, and hold the promise of improving human health, creating safer and more abundant food sources, and significantly contributing to the US economy.

VII. Appendix: Meetings used to gain scientific insight and support

The IWG has both benefited from and held several meetings over the past year that have addressed the need to pursue a genomics program for domesticated animals. Table 2 provides a summary. USDA, NIH, DOE, and NSF sponsored a National Research Council workshop titled "Exploring Horizons for Domestic Animal Genomics," which was organized by the Board on Agriculture and Natural Resources, Board on Life Sciences. The meeting was held on February 19, 2002, in Washington, D.C. The summary of the workshop has been published by the National Academy Press and is available at: <http://www.nap.edu/catalog/10487.html>.

Dr. Joseph Jen was invited to speak about the IWG and a national program in Domestic Animal Genomics at the Southeastern Stakeholders Listening Session, NASULGC Food and Society Project in Athens, GA on June 3, 2002. Genomics had previously been identified as a critical element within the Food and Society Project's Food and Environment division as a field with increased potential for researchers and long-term benefit to the agricultural community.

Dr. Chen Zhu, Vice President of the Chinese Academy of Sciences, and Dr. Cao Jinghua, Director and Professor, Office of American and Oceanian Affairs, Bureau of International Cooperation, Chinese Academy of Sciences, met with the IWG as well as other Government scientists on June 24, 2002 in Washington, D.C. The Chinese participated in the human and rice international genome projects, and have also sequenced several microbes. They are currently pursuing new partnerships to sequence the pig genome. This meeting was followed by a U.S. delegation to Beijing, China, July 31-August 1, 2002, to discuss forming a collaborative program in pig genomics. Dr. Joseph Jen led the delegation, which included IWG members Drs. Cliff Gabriel and Jane Peterson, as well as USDA/ARS scientists Drs. Steve Kappes and Gary Rohrer. The delegation visited the Beijing Genome Institute, the National Center for Human Genome Research, the Ministry of Science and Technology, and the Chinese Academy of Sciences. The scientific meetings led to a draft research proposal for a bilateral collaboration to sequence the Duroc, a breed common in the U.S.

The IWG has also held two roundtable discussions with stakeholders. The first meeting, on September 3, 2002, was comprised of representatives from the animal feed, breeding, and biotechnology industry, all members of the Alliance for Animal Genome Research. On October 11, 2002, the IWG held a meeting with academic and government researchers, including directors of genome sequencing centers. All attendees supported the mission statement and goals developed by the IWG. At both meetings, the IWG was urged to draw attention to the need





to invest in domestic animal genomics as the lack of tools available to animal researchers that biomedical, plant and microbe researchers now rely upon was compromising the discovery potential in animal science. Given the potential benefits to human health, the food supply, and the economy, it is critical to develop a strategic program to place domesticated animals on the agenda. The private sector felt that current investment in genomics was the role of the Federal government, however the Alliance for Animal Genome Research has been pursuing international funding sources to support large-scale genome sequencing.



Table 2. Chronological summary of activities regarding domestic animal genomics.

January 2, 2002	Presentation by Dr. Joseph Jen, USDA to the Committee on Science, National Science and Technology Council
February 19, 2002	Exploring Horizons for Domestic Animal Genomics Workshop, National Research Council
March 14, 2002	Interagency Working Group on Domestic Animal Genomics chartered
May 29, 2002	Inaugural IWG meeting
June 3, 2002	Presentation by Dr. Joseph Jen and Dr. Leland Ellis about the IWG to the Southeastern Stakeholders Listening Session, NASULGC Food and Society Project, Athens, GA
June 24, 2002	IWG meeting with guest Dr. Chen Zhu, Vice President of the Chinese Academy of Sciences
July 11, 2003	IWG meeting
July 31-August 1, 2002	IWG members travel to China, develop joint proposal for sequencing swine genome
September 3, 2002	IWG listening session with industry stakeholders
October 11, 2002	IWG listening session with academic and government researchers
May 16, 2003	IWG meeting

Acknowledgements

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Page vi Chicks, photo by Keith Weller, ARS image number K3627-16.

Page 1 Chicks atop a picture of a genetic map of a chicken, photo by Peggy Greb, ARS image number K8764-1.

Page 2 Pigs, photo by Keith Weller, ARS image number K7974-18.

Page 3 Top: Differences between European and Africanized honey bees can be seen in this DNA sequencing gel being read by microbiologist Hachiro Shimanuki and geneticist Cristina Arias, photo by Scott Bauer, ARS image number K5764-16. Bottom: Cat on human conserved synteny map, National Cancer Institute.

Page 4 Cattle feeding, photo by Brian Prechtel, ARS image number K5643-20.

Page 5 Top: White turkey, photo by Scott Bauer, Agriculture Research Service image number K7043-16. Bottom: Husky, photo by Julie Beth Zimmerman.

Page 6 Top: Cat genome physical map, National Cancer Institute. Bottom: Entomologist Steve Sheppard prepares an agarose gel to be used in separating honey bee DNA fragments, photo by Scott Bauer, ARS image number K5799-1.

Page 7 Top: Boxer, Whitehead Institute/MIT Center for Genome Research. Bottom: Lamb, photo by Karen Carpenter, Texas A&M University.

Page 8 Top: Cat/Human Parallel Radiation Hybrid Map, National Cancer Institute. Bottom: Dairy cow, photo by Keith Weller, ARS image number K5176-3.

Page 9 Top: Jack Russell terrier, photo by Dave Hodge. Bottom: Siamese cat, photo by Ann Carlson.

Page 10 Horse at pasture, photo by Tim McCabe, USDA image number 80cs0447. Chickens, photo by Joe Valbuena, USDA image number: 95cs1971.



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